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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,137	10/03/2005	Kevin Jeffrey Barnham	18803	4715

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ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,137	BARNHAM ET AL.	
	Examiner	Art Unit	
	JEFFREY H. MURRAY	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *1-21,23-25,33 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-32* is/are rejected.

7)☒ Claim(s) *22 and 26-29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/26/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. This action is in response to a restriction election response filed on May 27, 2008. Applicants have elected Group II with traverse. There are thirty-four claims pending and eight claims under consideration. Claims 1-21, 23-25, 33, and 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 27, 2008. This is the first action on the merits. The present invention relates to neurologically-active compounds, processes for their preparation and their use as pharmaceutical or veterinary agents, in particular for the treatment of neurological conditions, more specifically neurodegenerative conditions such as Alzheimer's disease.

2. Applicants have elected Group II with traverse in an action dated May 27, 2008. The applicants argue that Group II should not be restricted as they do not believe there are patentably distinct species within the application. This is not found persuasive. The claims of Groups I-IX and XI deal with several different compounds.

In the instant case numerous compounds are directed to structurally dissimilar products such that the variable core that exists within the two claims does not belong to a recognized class of chemical compounds in the art, and references that exist in anticipating one invention would not render obvious the others. For example, a quinazolin-8-ol compound is structurally dissimilar to a 1,7-phenanthrolin-6-ol compound. Thus, separate searches in the literature would be required. Each group's

compounds are made and used independently of each other and could support separate patents. The compounds differ significantly in chemical structures. One skilled in the art would not consider such diverse structures as functional equivalents of each other. The mere fact that there is a single similarity is not in itself a significant reason to render the whole embodiment obvious. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. The examiner has determined that select compounds or compositions of Formula Ia seen in claims 22, 26-29, and 32 should be considered under elected Group II. Therefore, claims 22 and 26-32 will be examined on the merits for compounds or compositions of Formula Ia. The applicant's arguments are not found persuasive. Therefore, the restriction requirement is deemed proper and is therefore made **FINAL**.

Priority

3. Acknowledgment is made of Applicant's claim for domestic priority. This application 10/530,137, filed October 3, 2005, is a national stage application of PCT/AU03/01303, filed October 3, 2003, which claims foreign priority to Australian Application No. 2002951864, filed September 23, 2002; Australian Application No. 2002951865, filed September 23, 2002; Australian Application No. 2002951866, filed September 23, 2002; and, Australian Application No. 2002951868, filed September 23, 2002.

Specification

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

5. Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." In the instant application, there is a very specific compound (only one) and a very specific use (only one) seen within the claims. As the claims embrace only one species compound used to treat one specific disorder, the abstract is too broad.

Complete revision of the content of the abstract is required on a separate sheet.

6. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

Claim Objections

7. Claims 26-32 are objected to because of the following informalities:

Claims 26-32 are objected to for containing non-elected subject matter within the claims. Appropriate correction is required.

8. Claim 22, 26-29 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only, and/or, cannot depend from any other multiple dependent claim. See MPEP

§ 608.01(n). Accordingly, the claims 22, 26-29 have not been further treated on the merits.

9. Claim 31 contains the phrase, "Compounds..." This is not proper because it must be singular. Applicants are entitled to only one invention, not multiple inventions. Examiner suggests rewriting the claim to read, "A compound..." Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

110. Claims 30-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound, composition, pharmaceutically acceptable salt or tautomer, does not reasonably provide enablement for hydrates, solvates, derivatives, pro-drugs, and/or isomers; or, the compounds, compositions, salts or tautomers where R^1, R^2 or R^3 is an "antioxidant" or a "targeting moiety". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

12. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (*United States v. Teletronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a

single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

1) *Amount of guidance provided by Applicant.* Applicant has provided no guidance, examples, or provided any chemical or biological data and/or testing results of any compounds that fall outside of the scope previously mentioned or of any hydrates, solvates, derivatives, pro-drugs, and/or isomers; or, the compounds, compositions, salts or tautomers where R^1, R^2 or R^3 is an "antioxidant" or a "targeting moiety" in the current application.

The quantity of experimentation needed to make or use the invention must be considered to determine if undue experimentation is present. With regard to quantity of experimentation needed, note Wolff et. al., provided with this action, which emphasizes the many experimental factors for consideration for a successful prodrug as well as the difficulty in extrapolating data from one species to another. See p.975-7. "Extensive development must be undertaken to find the correct chemical modification for a specific drug. Additionally, once a prodrug is formed, it is a new drug entity and therefore requires extensive and costly studies to determine safety and efficacy." Banker, et. al., Modern Pharmaceuticals, p.596. In view of all these factors undue experimentation would be required to practice the invention.

The Applicant has demonstrated within the application how to make a number of quinazoline compounds and compositions, however, applicant has not demonstrated any of the thousands of potential hydrates, solvates, derivatives, pro-drugs, and/or

isomers; or, compositions, salts or tautomers where R^1, R^2 or R^3 is an "antioxidant" or a "targeting moiety" that have been claimed outside of this minute scope.

2) Unpredictability in the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. (USPQ 18, 24 (CCPA 1970). See *In re Fisher*, 427 F.2d 833, 839, 166.

Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

The scope of "hydrate" and "solvate" is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. Solvates cannot be predicted and there fore are not capable of being claimed if the

applicant cannot properly enable a particular solvate.

> "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates. Vippagunta et. al. Advanced Drug Delivery Reviews 48 (2001) 3-26.

The scope of esters or prodrugs is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. The choice of an ester or prodrug will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which ester or prodrug will be suitable for the instant invention. The application does not provide any guidance for one skilled in the art on how the ester or prodrug is converted to active compounds, by what mechanisms and at what site the ester or prodrug will be activated, what *in vivo* enzymes are likely involved in cleaving the protected group, etc.

Applicants provide no reasonable assurance that any and all known esters will have the ability to regenerate in *vivo* to the instant compounds by one or more biological processes. It is not the norm that one can predict with any degree of accuracy a particular ester form of an active compound will be more soluble, more easily handled in formulations or more bioavailable without actual testing *in vivo*.

Many functional groups (eg. hydroxy,amino groups) present in drugs are capable at least in theory to being derivatized but determining what is an *in vivo* hydrolysable ester (and what is not) requires knowledge of an intended effect (i.e. modification of an undesirable property in the parent drug- poor solubility, poor bioavailability, poor shelf-life) which is never identified by the specification.

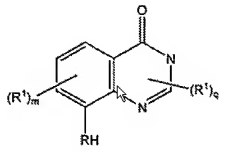
""Isomers" and "derivatives" literally would include billions of additional compounds covered by the claims' scope that may (isomers) or may not (derivatives) have the same molecular formula. In the absence of any guidance in the specification, nothing short of extensive synthesis and testing would be needed to determine if any such "isomeric" or "derivatized" compounds would have the activity needed to practice the invention.

3) *Number of working examples.* The compound core depicted with specific substituents represent a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed or preventive agents. Applicant has provided no working examples of any hydrates, solvates, derivatives, pro-drugs, and/or isomers; or, compositions, salts or tautomers where R^1, R^2 or R^3 is an "antioxidant" or a "targeting moiety".

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula

of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

4) *Scope of the claims.* The scope of the claims involves all of the compounds of Formula Ia of claim 4 with the following general formula:



thus the scope of the claims is broad.

5) *Nature of the invention.* The present invention relates to neurologically-active compounds, processes for their preparation and their use as pharmaceutical or veterinary agents, in particular for the treatment of neurological conditions, more specifically neurodegenerative conditions such as Alzheimer's disease.

6) *Level of skill in the art.* The artisan using Applicants invention would be a chemist with a M.S. or Ph.D. degree, and having several years of bench experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That

conclusion is clearly justified here that Applicant is not enabled for treating the disease mentioned.

Claim Rejections - 35 USC § 112, 2nd paragraph

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 30-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. The scope of "aryl," "heterocyclyl," "antioxidant" and "targeting moiety" requires clarification since applicants' examples in the specification are not limited in any way. See definitions on p.18-20 of the specification. Where applicants define terms with a special meaning, they must set out the special definition with "reasonable clarity, deliberateness and precision". Note *Teleflex v. Ficosa*, 63 USPQ2d 1374; Rexnord Corp v. Laitram Corp. 60 USPQ2d 1851 and MPEP 2111.01.

In the absence of the specific moieties intended to effect modification by "substitution" or attachment to the chemical core claimed, the term "substituted" renders the claim in which it appears indefinite in all occurrences wherein applicant fails to articulate by chemical name, structural formula or sufficiently distinct functional language, the particular moieties applicant regards as those which will facilitate substitution, requisite to identifying the composition of matter claimed.

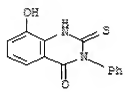
Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Lauenstein, et. al., Biochimica et Biophysica Acta (1956), 21, 587-8. The prior art teaches the following compound:

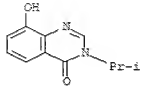
RN 106590-28-3 CAPLUS
CN 2,4(1H,3H)-Quinazolinedione, 8-hydroxy-3-phenyl-2-thio- (6CI) (CA INDEX NAME)



Which is a tautomer of a compound of Formula Ia where RH is OH; q=2; where one R^1 is S-R^2, and R^2 is hydrogen; and the second R^1 is a phenyl ring.

18. Claims 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Iyer, et. al., Journal of Scientific & Industrial Research (1956), 15C, 1-7. The prior art teaches the following compound:

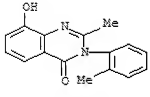
RN 104296-29-9 CAPLUS
CN 4(3H)-Quinazolinone, 8-hydroxy-3-isopropyl- (6CI) (CA INDEX NAME)



Which is a compound of Formula Ia where RH is OH; q=1; and R^1 is an isopropyl group.

19. Claims 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Nowak, et. al., Journal Arzneimittel-Forschung (1966), 16(3), 407-11. The prior art teaches the following compound:

RN 5060-53-7 CAPLUS
CN 4(3H)-Quinazolinone, 8-hydroxy-2-methyl-3-(2-methylphenyl)- (CA INDEX NAME)



Which is a compound of Formula Ia where RH is OH; q=2; where one R^1 is a methyl group and the second R^1 is an *o*-tolyl group.

Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 30-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent Publication Application No. 2008/0119470. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of U.S. Patent Publication Application No. 2008/0119470 embraces the instant claims 30-32.

The instant claim differs from the copending claim by a more limited genus than the claim of the copending application. However, it would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus of the copending application, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus of the copending application since such compounds would have been suggested by the claims of the copending application. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

22. Claims 30-32 are rejected.

23. Claims 22 and 26-29 are objected.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is (571) 272-9023. The examiner can normally be reached on Mon.-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey H Murray/
Patent Examiner
Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624